However, in paragraph 6, on page 1 of the Office Action, the Examiner indicates that Claims 8-16 have been rejected.

In particular, in paragraph 4, on page 2 of the Office Action, the Examiner rejects Claims 8-16 under 35 U.S.C. § 102(a) as being anticipated by Sempere et al (1999).

Specifically, the Examiner states that Sempere et al (1999) teaches using a *Polypodium* extract to modulate the expression of adhesion molecules.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants claim benefit of Spanish Application P9900182, filed January 25, 1999, which is prior to the December 1999 publication date of Sempere et al (1999). Thus, in view of the sworn translation into English of the Spanish priority document provided herewith, it is clear that Sempere et al (1999) is not prior art. Thus, Applicants request withdrawal of the Examiner's rejection.

In paragraph 5, on page 3 of the Office Action, the Examiner rejects Claims 15-16 (directed to a method for immuno-modulation) under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,601,829 (hereinafter "US '289").

Applicants hereby cancel Claims 15-16 without prejudice or disclaimer, thereby rendering moot the Examiner's rejection.

In paragraph 6, on page 3 of the Office Action, the Examiner rejects Claims 8-16 under 35 U.S.C. 102(b) as being anticipated by Sempere et al (1997).

Specifically, the Examiner states that Sempere et al (1997) teaches using Anapsos to reduce inflammation and modulate the

immune system (see page 88 thereof). The Examiner notes that Sempere et al (1997) does not specifically teach that Anapsos inhibits expression of adhesion molecules. However, it is the Examiner's position that adhesion molecules are an essential part of the inflammatory response, and that since Sempere et al (1997) teaches administering Anapsos to reduce inflammation, the method taught therein would inherently have the effect of reducing expression of adhesion molecules.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Claims 8-12 are directed to a method of inhibiting expression of an adhesion molecule; and Claims 13-14 are directed to a method of inhibiting inflammation. As noted above, Claims 15-16 have been cancelled without prejudice or disclaimer.

The Examiner is requested to note that the inflammatory response is a complex process due to multiple factors. Indeed, not only adhesion molecules or cytokines are responsible of inflammation, but also mechanisms exist through some membrane lipid derivatives, arachidonic acid derivatives, prostaglandins, leucotrienes and platelet activator factor, plasmatic proteases (Kinin system, Complement system), nitric oxide synthase, etc.

Sempere et al (1997) may suggest that the *Polypodium* extract reduces the expression of adhesion molecules that are overexpressed by induction of cytokines. While some drugs are able to reduce the overexpression of some adhesion molecules induced by cytokines, some drugs have no effect on other adhesion molecules (Heimburger et al, *Biochem. Pharmacol.*,

56(12):1661-1669 (1998), a copy of the Abstract for which is attached hereto).

The experiments carried out by Sempere et al (1997) were *in vitro* experiments. Sempere et al (1997) used LPS (lipopolysacharide) or LPS+PHA (phytohaemaglutinin) to stimulate the production of cytokines, and then compared the results obtained with those obtained after adding *Polypodium* extract (Anapsos) to the cultures. LPS is normally used to stimulate the macrophage population which produces proinflammatory cytokines. An increase in the cytokine levels can cause a parallel overexpression of some adhesion molecules. Thus, the decrease in some of the proinflammatory cytokines after adding *Polypodium* to the cultures, observed by Sempere et al (1997), may be due to the down-expression of some of the adhesion molecules.

However, the effect of Anapsos on the expression of adhesion molecules claimed in the present application is very different and is observed both *in vitro* (Example 3) and *in vivo* with healthy humans (Example 4).

One of the most important differences between Sempere et al (1997) and the present invention is that the *in vitro* experiments carried out by Applicants, with PBMNc (Peripheral Blood Mono-Nuclear cells) from healthy controls, were not obtained by stimulation with LPS, but by stimulation with PHA, at different concentrations. Therefore, an increase in proinflammatory cytokines levels is not likely to arise in the Examples of the present application, nor the existence of an indirect effect mediated by *Polypodium* through a potential

decrease/impairment of PHA-stimulated cytokine levels, which would cause the down-expression of adhesion molecules. Thus, an additional or independent effect of *Polypodium* on the expression of adhesion molecules can not be discarded, for example, mediated by a mechanism through the intervention of transcription factors. In fact, one of the most studied transcription factors, NF-kB, is involved in the induction of many genes encoding many proteins, including adhesion molecules. Additionally, some well-known medicines, like corticosteroids, act on inflammation by blocking different targets in an independent way, such as by means of mechanisms that involve arachidonic acid derivatives, nitric oxide sinthase (NOS), proinflammatory cytokines and adhesion molecules, which are probably all of the effects mediated by a common NF-kP inhibitor (Barnes et al, *Trends Pharmacological Sciences*, 14(12):436-441 (1993), a copy of the Abstract of which is attached hereto).

Moreover, the differences between the *in vitro* experiments of Sempere et al (1997) and the present invention are shown in Example 3, where a notably down expression of CD11b (14%), in relation with the respective control (20%), is seen after adding the *Polypodium* extract to the PBMNc cultures. Therefore, it is clear that the *Polypodium* extract, apart from its inhibiting activity on some proinflammatory cytokines (that may partially explain a decrease of certain adhesion molecules), also independently inhibits a direct effect on the spontaneous expression of these molecules, as shown by the results in Example 3.

Applicants also studied the effects of the *Polypodium* extract *in vivo*, which are the results shown in Example 4. As shown in this example, a down-expression of CD11a and CD11b in PBMNc is observed after the administration of *Polypodium* extract. This effect is not due to *Polypodium* decreasing proinflammatory cytokines. This is because the experiments were performed with healthy voluntary humans, in which it is expected to find normal levels of proinflammatory cytokines, since there exists no inflammation. When serum levels of proinflammatory cytokines were measured, Applicants did not observe an ability of the *Polypodium* extract to significantly decrease the aforementioned cytokine levels, whereas a decrease of the adhesion molecules was seen.

Thus, one skilled in the art could not have reasonably expected from Sempere et al (1997) that the *Polypodium* extract of the invention would directly modulate the expression of adhesion molecules.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Sempere et al (1997), and thus request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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A P P E N D I X

Marked-up Version of Changes

IN THE CLAIMS:

Claims 15-16 are being cancelled.